



46
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EXAMINER

TON, THAIAN N

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/015,948

Applicant(s)

ALLEN ET AL.

Examiner

Thaian N. Ton

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 June 2005.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,9-18 and 20-44 is/are pending in the application.
- 4a) Of the above claim(s) 1,2,10-13 and 29-38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 9, 14-18, 20-28, 39-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

502

DETAILED ACTION

Applicants' Petition under 37 CFR §1.137(b)(3) to revive an unintentionally abandoned application was granted on 8/17/05.

Applicants' Amendment and Response, filed 6/20/05, have been considered. Claims 9, 14, 15, 17, 18, 20, 21, 23, 26 and 27 have been amended; claims 39-44 have been added; claims 1, 2, 10-13, 29-38 are withdrawn; claims 9, 14-18, 20-28, 39-44 are under current examination.

Election/Restrictions

Claims 1, 2, 10-13, 29-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/31/03.

Applicant's election without traverse of Group II in the reply filed on 7/31/03 is acknowledged.

Specification

The amendment filed 6/20/05 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. §132 states that no amendment shall introduce new matter into the disclosure of the invention.

Applicant has amended the specification at page 12, line 29, to incorporate US Provisional Application 60/084,194. This reference is not considered new matter because the original specification incorporated USSN 08/971,310 by reference, which was converted to the Provisional Application 60/084194. However, the additional references are considered new matter. The references include a second provisional application (60/084,949), a utility application claiming priority to the two provisional applications (09/193,834) and a second utility application that is a continuation of the first utility application (09/885,816; published as US Patent

6,815,185). There is no evidence that these newly referenced applications were contemplated as being part of the original specification as an incorporation by reference. The reference to "U.S. Patent no. 6,815,185 issued November 9, 2004, which is based on U.S. Patent Application No. 09/885,816, filed June 19, 2001, which is a continuation of U.S. Application No. 09/193,834, filed November 17, 1998, now abandoned, which claims priority to provisional application no. 60/084,949, filed on May 11, 1998, and provisional application no. 60/084,194, the disclosure of provisional application no. 60/084,194" should be replaced with "US Patent Application No. 08/971,310, which was converted to provisional application no. 60/084194". The other applications should not be included.

New Matter

Claims 9, 14-18, 20-28, 39-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

The amended claims include the following new matter:

Null allele. As amended, the claims recite, "a null ACTHR allele", but the as-filed specification does not provide support for said "null allele". Given its broadest reasonable interpretation, the term "null allele" is understood to refer to any disruption that (i) inactivates a gene, so that no gene products are expressed from the inactive allele, (ii) produces an active allele that encodes a non-functional mRNA product that does not produce a protein product, or (iii) produces an active allele that encodes a functional mRNA product that produces a non-functional

protein product. However, the instant specification does not describe a mouse having a null allele, but rather refers to a "null disruption, wherein this is no significant expression of the ACTHR gene." See p. 8, lines 4-5. However, the term "null allele" is much broader and not contemplated in the specification as originally filed. Applicants have not pointed to any support in the as-filed specification for the amendment, and absent specific support in the as-filed application, the newly recited terms constitute new matter.

To the extent that the claimed invention is not described in the instant disclosure, claims 9, 14-18, 20-28, 39-44 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described. See also, MPEP §2163.06 MPEP §2163.02.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Definitions:

[from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from <http://www.uspto.gov/web/menu/utility.pdf>]

"Credible Utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong". Rather, Office personnel must determine if the assertion of utility is credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic

underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A *credible* utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests (see below).

"Specific Utility" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

Art Unit: 1632

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

Note that "throw away" utilities do not meet the tests for a *specific* or *substantial* utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are "throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. ' 101. This analysis should, of course, be tempered by consideration of the context and nature of the invention. For example, if a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial *asserted* utility would be considered to be met.

"Well established utility" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. "Well established utility" does not encompass any "throw away" utility that one can dream up for an invention or a nonspecific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. If this is the case, any product or apparatus, including perpetual motion machines, would have a "well established utility" as landfill, an amusement device, a toy, or a paper weight; any carbon containing molecule would have a "well established utility" as a fuel since it can be burned; any protein would have well established utility as a protein supplement for animal food. This is not the intention of the statute.

See also the MPEP § 2107 - 2107.02.

Claims 9, 14-18, 20-28, and newly added claims 39-44 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. This rejection is maintained for reasons of record advanced in the prior Office action.

Applicants argue that claim 14 is now amended to a transgenic mouse whose genome comprises a null ACTHR allele, comprising exogenous DNA, and thus, Applicants argue that the claimed invention has utility because, where an invention

has a well-established utility or is useful for any particular practical purpose, the invention fulfills this standard. Applicants argue that the present invention has a well-established utility since a person of ordinary skill in the art would immediately appreciate why knockout mice are useful. Applicants argue that in general, a knockout mouse has the inherent and well-established utility of defining the function and role of a disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations, or properties of the knockout mouse. Applicants argue that the NIH has stated that the knockout mouse is the premier model for determining gene function, and assert that this is a utility that is specific, substantial, and credible. Finally, Applicants argue that knockout mice are so well-accepted as tools for determining gene function, that various individuals have proposed creating knockout mice for all genes. See pp. 8-11 of Applicants' Response. Applicants argue that with respect to the claims drawn to transgenic mice having a null allele, Applicants provide Austin *et al.*, who state that null-reporter alleles should be created, that they are an, "indispensable starting point for studying the function of every gene." Further, Applicants argue that research tools, such as the instantly claimed knockout mice, are patentable because they have a clear, specific and unquestionable utility, which is to analyze gene function. Applicants further argue that various authors provide support for the asserted utility of the claimed mice, for example, Alberts *et al.* provide teachings to show that knockout mice are "invaluable tools for investigating gene function," Genes VII states that knocking out of a gene is, "[A] powerful method to investigate directly the importance and function of the gene." See pp. 11-13 of the Response. Applicants submit that one of ordinary skill in the art would immediately recognize the utility of a knockout mouse in studying gene function, and that this utility is found to be specific, substantial, and credible. See p. 13-14 of the Response.

This is not persuasive. In the instant case, the claimed knockout mice lack utility for the reasons set forth in the previous Office action. For example, knockout

mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. However, the contemplated utilities of using the instant mice to obtain a clue to a pathway is not a considered "substantial utility. Although it was scientifically well-known to knock out a gene to determine its function, or what would happen when the gene is not expressed, scientific "utility" is not the same as "patentable utility" or a "well-established" utility. The MPEP and utility guidelines clearly set forth that a "well-established utility" must be specific, substantial and credible. At the time of filing, knockout mice were used for further research in the art. However, further research does not rise to the level of a "well-established utility" because such a utility is not substantial or specific.

With respect to MPEP §2107.01, I (see p. 12-13 of Applicants' Response), a gas chromatograph is a research tool with a well-defined function and highly specific use that does not necessitate further study of itself. It may be that a gas chromatograph may be used for a wide variety of analyses; however, this does not change its specific use for analyzing a sample. In contrast, the claimed invention is not a general tool for analyzing other samples and, at most, serves to study the function of a single gene. In this respect, the utility of a knockout mouse cannot be compared to a gas chromatograph. Therefore, the utility of the instant invention is neither specific nor substantial.

The utility guidelines specifically state that further research is not a "substantial utility":

[T]he following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

In this case, further study of mice would have been required to determine how to use the mouse of Applicants' invention as a model of disease, particularly, because there is no nexus between the observed phenotypes of the claimed mice, and a FGD, which is observed in patients with mutations of ACTHR. FGD has various phenotypes, including hyperpigmentation, hypoglycemic episodes, failure to thrive, and frequent and severe infections. The instantly claimed mice are observed to have broad phenotypes of an adrenal gland abnormality, and in specific embodiments, decreased cytoplasmic vaculation in brown adipose tissue, when compared to wild-type mice, additionally the mice show a metabolic abnormality, an increased susceptibility to seizure, increased activity, and anti-depressive behavior. There is no correlation between the observed phenotypes of the claimed mice and that of FGD, and thus, one of skill in the art could not use these mice as models of this disease. Therefore, further study and experimentation would be required in order to determine the association of a disruption of ACTHR allele with a specific condition. Note that it is clear from all of the art provided by Applicants that knockout mice are used to elucidate gene function, which is not considered a substantial utility.

Applicants note that in the prior Office action, the Examiner has imposed a rejection of the claimed mouse for obviousness. Applicants argue that the Examiner cannot maintain the contradictory position that one of ordinary skill would have been motivated to make the claimed mouse, but the argue that the same ordinarily skilled artisan would not know how to use the mouse, once created. Thus, Applicants argue that the Examiner's statements are effectively an admission that the claimed invention satisfies the utility requirement. See p. 14 of the Response.

This is not persuasive. As stated previously, scientific obviousness is not an indication of patentable utility. The motivation stated under the §103 rejection is directed to determine the physiological role of a gene. However, determination of

the role of a gene does not constitute a patentable utility, as this would require further research.

Applicants argue that the disclosed phenotype of the claimed mice provide utility to the claimed mice. Applicants assert that the instant case is similar to arguments made in *In re Brana*. Applicants argue that the claimed invention is useful for a practical purpose, and that this assertion would be considered credible by a person of ordinary skill in the art; because the claimed mice have demonstrated specific phenotypes and the use of these mice would be considered to be an unbelievable undertaking or to involve implausible scientific principles. Applicants cite art to show that knockout phenotypes provide accurate information concerning gene function (Doetschman). See pp. 14-16 of the Response.

In response, the fact pattern in *Brana* does not correlate to the fact pattern of the instant application. In *Brana*, the court addressed two separate issues, utility and enablement. The court held that the specification did, in fact, disclose a specific and substantial use for the compound, treating leukemia, and that this use was overlooked by the PTO in making the rejection under §101. The court observed that the claimed compound was similar in structure to compounds in the prior art that were useful in treating leukemia. The claimed compound behaved in a manner similar to that of the prior art in art accepted assays for anti-leukemic activity. Therefore, the specification enabled the use. The instant specification and the art of record fail to support such a patentable utility for the instant invention and therefore, the principles set forth in *In re Brana* do not apply to the instant invention. Furthermore, it is reiterated that the instant invention does not have utility because the mice exhibit a phenotype that fails to be correlated to a particular disease or condition associated with the ACTHR gene of the claimed invention.

Applicants argue that definitive proof that the phenotypes observed in the null mouse would be the same as those observed in humans is not a prerequisite to

satisfying the utility requirement and that it is enough that the claimed mouse demonstrates a phenotype, relative to a wild-type control mouse, and that knockout mice are recognized as models for determining gene function. Applicants cite Austin to show that mice have much in common with human and that the utility requirement only requires that an asserted utility be credible to one skilled in the art. Applicants argue that it is not necessary to prove that a definitive link exists between the target gene and the observed phenotype(s); and that the use of knockout mice to predict and understand gene function in humans is well-accepted and established in the art. Applicants argue that further research would not be required to confirm the utility of the claimed mice in determining the function of the ACTHR gene, and that the value of knockout mice in determining gene function is well-established and accepted in the art. Applicants argue that the Examiner is improperly applying the MPEP definition for "substantial utility" because the knockout mice have a well-known use, to study gene function, and thus, the invention fulfills the requirement for utility. Applicants argue that the Examiner needs to differentiate between the utility of the claimed mouse, and the utility of the target gene; the latter of which is not being claimed. See p. 17-19 of the Response.

This is not persuasive. As shown in previous Office actions, under §112, 1st paragraph, the phenotypes of mice is not predictive nor is it necessarily correlated to what is observed in humans. Although mice and humans may have many diseases, genes, or physiology in common, the art does not support that this would be predictive of the phenotype that results in the knockout of a mouse's endogenous gene. Finally, it is reiterated that the claimed mice do not have a specific utility, as Applicants are referring to a general utility, to use a knockout mouse to study gene function. Furthermore, this is not found to be a substantial utility, as further experimentation and characterization would be required in order to determine what

the phenotypes observed in the knockout mouse relate to the gene that is knocked out.

Applicants argue that the link between the ACTHR gene and a disease or disorder is not required to satisfy the utility requirement. The phenotypes of the mice, as determined by the mice in the tests in the specification, reasonably correlated to disease states, such as seizure and depression, and that no further research is required to establish any use for the claimed mouse. Applicants argue that whether additional research is required to identify therapeutic agents targeting the ACTHR gene, or to further characterize the function of the ACTHR gene, is irrelevant to whether the claimed invention has satisfied the utility requirement. See p. 19 of the Response.

This is not persuasive. The specification fails to provide a nexus between the knockout of the ACTHR gene and the observed phenotypes. The art teaches particular phenotypes that are observed in humans in mutations of the ACTHR gene. In order for the claimed mice to have specific utility, their utility would have to be specific to the ACTHR gene. Thus, the phenotypes exhibited by the claimed mice must be reasonably correlated to the function (or lack thereof) of the ACTHR gene. Applicants fail to provide a specific correlation between the specific biological activity of ACTHR and a specific disease condition, and thus, as supported by the MPEP, this lacks specific utility for the invention. See MPEP §2107.

Applicants argue that in addition to being used to study gene function, the claimed transgenic mice are useful for studying gene expression, for example, using a marker such as lacZ. The claims as amended now recite that the transgenic mice contain a selectable marker, such as lacZ. Applicants cite Austin *et al.* to support that studying gene expression using a reporter gene is clearly recognized by those skilled in the art. Further, Applicants remind the Examiner that the claimed invention need only satisfy one of its stated objectives to satisfy the utility and enablement requirements. See p. 19-20 of the Response.

This is not persuasive. In particular, utilizing a visible marker, such as lacZ is a general utility that applies to any knockout mouse and is not specific. It is a widely used technique to generate mouse knockouts by inserting a visible reporter gene into an endogenous gene. Just as any gene can be cloned to study gene expression, any gene can be knocked out using a lacZ construct to study function and/or expression.

In light of the above, the skilled artisan would not find the asserted utility of the transgenic mouse and cells encompassed by the claims to be specific or substantial.

Claims 9, 14-18, 20-28, 39-44 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 9, 14-18, 20-28, and newly added claims 39-44 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants traverse this rejection, and state that the claimed invention has credible specific and substantial utility, and that therefore, one of skill in the art would be able to practice the claimed invention without undue experimentation. Applicants argue that they disagree with the prior rejection, with regard to the unpredictability of a phenotype in a resultant transgenic animal. Applicants argue that any phenotype associated with the mice would be consistent and inherent to the mice, and that the general rule of disruption of the coding sequence by a positive selection marker, as taught by the instant specification, will result in a null allele, which, by definition, involves the ablation of gene function. Applicants argue that predicting a phenotype should be distinguished from the reproducibility of the phenotype. Unexpected or unanticipated phenotypes, such as those disclosed in Moreadith, are well-known in the art. Applicants argue that they have described the production of a transgenic mouse, and the phenotypic characteristics of the mouse, therefore, the issue of predicting a phenotype is not relevant, particularly because the null disruption would be expected to result in a reproducible phenotype, the specification clearly enables a person of skill in the art to make and use the transgenic mouse. See pp. 20-21 of the Response. Applicants argue that the phenotypes that are instantly claimed are reasonably correlated to disease states or conditions, such as epilepsy, seizure, depression, or hyperactivity. Furthermore, Applicants argue that the claimed transgenic mice would be considered useful to person of skill in the art, regardless of the phenotype, because the mouse is useful for determining the function of the ACTHR gene, and for the analysis of gene function. Thus, Applicants conclude that the skilled artisan would be clearly enabled by the specification to make and use the null ACTHR mouse, as instantly claimed. See p. 22 of the Response.

This is not found to be persuasive. The claimed invention is directed to a ACTHR knockout mouse. The art of record clearly shows that the phenotype of knockout mice is exceedingly unpredictable. The lack of correlation between the

resultant phenotype and knockout of the ACTHR gene fails to provide an enabled use for the claimed mice, as one of skill would not know what to use these mice for. For example, the art teaches particular phenotypes that manifest upon the mutation of the ACTHR gene. There is no nexus between these art-recognized phenotypes and those observed in the instantly claimed transgenic mice. Furthermore, the unpredictability in phenotypes of resultant knockout mice, is often due to differences in the strains of mice. For example, Liu *et al.* [**Biol. Psychiatry**, 49(7): 575-81 (April 1, 2001)] tested the genetic differences in tail-suspension tests on 11 different inbred strains of mice, and found differences in response between strains, as well as between male and female mice. See p. 575, 1st column, Results. They specifically teach that, "Genetic differences have been found among inbred and outbred strains of mice measuring spontaneous duration of immobility in the TST [tail-suspension test]." See p. 576, 1st column, 1st full paragraph. They teach that there is significant differences between the mean duration of immobility in the TST (see Figure 1 and p. 577, 2nd column, Results). They teach that gender differences are also found, where female mice have longer immobility than male mice (see Figure 3, and p. 578, 2nd column). Inspection of Figure 6 of the specification reveals that the tail suspension test was only performed on male mice. The claims are not enabled because they are not limited to the observation of this phenotype only in male mice, there is no indication what "wild-type" mice the mutant mice are compared to, and the art-recognized strain differences in interpretation of TST results, fail to provide a nexus between the knockout of the ACTHR gene and the observed phenotype of increased propensity for depression.

The specification discloses a battery of tests that were conducted on disrupted mice, and on wild-type controls. However, there is no disclosure as to what is meant by the term "wild-type". This term encompasses littermates, same-strain non-littermates, different strains of mice, for example. The instant specification

Art Unit: 1632

teaches that homozygous mutant mice had small or absent adrenal glands, moderate to severe decreases in cytoplasmic lipid vacuolation, and heterozygous mice showed thymic atrophy. The specification teaches that homozygous female mice exhibited a lower than average body fat percentage, when compared to age- and gender-matched wild-type control mice. See Example 3. This supports the unpredictability in the art, with regard to the resultant phenotype. Furthermore, there is 1) no guidance as to what the term "wild-type" encompasses and 2) the breadth of the claims are directed to any sex of mouse, but the specification only supports that female mice had this phenotype. The specification teaches that the Metrazol test was administered to the mutant mice, and it was found that homozygous mutant mice required lower doses of Metrazol to exhibit characteristic seizure responses, possibly indicating an increased susceptibility to seizure. See pp. 55-56 and Figure 3. Figure 3 only represents male mice, there is no indication that female mice would also exhibit this phenotype, which the breadth of the claims encompasses. The specification teaches that in an open-field test, the homozygous mice displayed an increase in the total distance traveled during the open field test, and thus, indicate that the mice are hyperactive relative to wild-type mice. See p. 56 and Figure 4. Again, Figure 4 is directed to tests conducted on male mice, and there is no indication that the female mutant mice would have this same phenotype. The specification teaches that during a tail suspension test, the mutant mice, when compared to wild-type mice, exhibited an anti-depressant phenotype, because they exhibited a decrease in the total time spent immobile in the tail suspension test. See p. 57 and Figure 5. Again, Figure 5 is directed to tests conducted on male mice, and there is no indication that the female mutant mice would have this same phenotype. Applicants have failed to provide sufficient guidance with regard to the resultant phenotype of the mutant mice, such that one of skill in the art would recognize that the phenotypes of these mutant mice were predictable, and then, would know how to use these mutant mice.

Art Unit: 1632

It is noted that the art recognizes that the resultant phenotype, when producing knockout mice, is exceedingly unpredictable. For example, Leonard [**Immunological Reviews**, (148): 98-113 (1995)] disclose mice with a disruption in the *g_c* gene that was intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (Abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths [**Microscopy Research and Technique**, 41:344-358 (1998)] taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph). Thus, at the time of filing, the resulting phenotype of a knockout was considered unpredictable. This is supported by the art at the time of filing.

The present specification discloses that, "To investigate the role of ACTHR, disruptions in ACTHR genes were produced by homologous recombination." See p. 52, lines 16-17. A targeting gene construct, comprising sequences homologous to ACTHR and mice were produced by introducing the targeting construct into 129 OlaHsd ES cells to produce chimeric mice, and that F1 mice were generated by breeding with C57BL/6 mice. The disclosure teaches that F2 homozygous mutant mice were produced by intercrossing F1 heterozygous males and females (p. 52, lines 25-26). The specification fails to specifically disclose the method to produce the chimeric mice, as they could not be produced from an ES cell alone, and the specification provides no guidance with regard to the embryo strain that was used in conjunction with the ES cell to produce the chimeric mice. A chimeric mouse, by definition, arises from the combination of an ES cell and embryo, and would not be considered chimeric if it could arise directly from an ES cell. Thus, the specification is not enabling because there is no teaching with particular regard to the mouse

embryo strain that is used to make the chimeric mice. This deficit cannot be corrected by declaration.

In attempting to determine gene function through an analysis of physiological testing of mice comprising a disruption of a particular gene, in this case, ACTHR, distinguishing between a phenotype that is a result of gene loss, versus genes of the parental strain, becomes problematic. In the production of the instantly claimed mice, the specification, as outlined above, teach that the recombination construct is injected into 129/OlaHsd mouse ES cells to produce chimeric mice, and that F1 mice were generated by breeding with C57BL/6 mice. The disclosure teaches that F2 homozygous mutant mice were produced by intercrossing F1 heterozygous males and females (p. 52, lines 22-26). However, it is well-established in the art that the resultant homozygous mice will have some 129/OlaHsd genes, regardless of the outwardly appearance of the mice, due to the 129 knockout construct. F2 mice homozygous for the disrupted ACTHR gene have genotypes from two parents, 129/OlaHsd and C57BL/6, due to recombination events during gametogenesis (see Gerlai *et al.* (**Trends in Neuroscience**, 19(5): 177-181 (1996), especially page 178, lines 1-5). Thus, these mice are genotypically different from wild-type littermates, and thus, wild-type littermates do not make good controls for the null mice (see p. 178, col. 1, lines 6-18). This effect causes "linkage disequilibrium between the transgene and surrounding genes, producing a "hitchhiking donor gene confound." See Lariviere *et al.* (**J. Pharmacology**, 297(2); 467-473 (2001); especially p. 468, col. 1, 2nd ¶, lines 1-4). In order to overcoming the "hitchhiking effect, two remedies are suggested: testing a large number of mice (see Gerlai, page 178, 2nd column, lines 1-5) and many backcrosses (see Lariviere, p. 468, 1st column, 2nd ¶, lines 18-21). However, even with a large testing population, and multiple backcrossings, some of the 129/OlaHsd genome will remain. Thus, the behavioral and physiological effects, observed in the presently claimed ACTHR knockout mice, could be due to the 129/OlaHsd gene (see Gerlai, p. 179, 1st col., lines

9-17). Given the tests in the disclosure, there is no way to tell, and thus, determination of whether or not the phenotype of the mice is seen due to the disrupted gene, the 129 "hitchhiking" alleles, or by compensation by other C57Bl genes, cannot be determined from Applicants' data.

Thus, while Applicant have demonstrated differences between mice with ACTHR gene disruptions, and wild-type mice, in certain assays associated with adrenal gland abnormality, cytoplasmic lipid vacuolation in brown adipose tissue, seizure, and hyperactivity, there is no guidance as to how to use these data. In particular, the specification states that these results indicate that ACTHR may have a role in some unnamed disease, but "may" or is "suggestive of" clearly shows that the mice do not have an enabled use. If the mice have no enabled use, then the claims directed to tissues or cells from the mice, methods of making the mice, a targeting construct, and mouse ES cells, also have no enabled use. There is no disclosure for any of these claims, other than as they relate to making the mice.

Accordingly, in view of the lack of teachings or guidance provided by the specification with regard to the correlation of the claimed phenotypes and the disruption of the ACTHR gene, the state of the art, with regard to the unpredictability in phenotype when producing knockout mice from different strains, it would have required undue experimentation for one of skill to practice the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 9, 14, 28 and newly added claims 39-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi [cited in the prior Office action] when taken with Kubo [cited in the prior Office action]. This rejection is maintained for reasons of record advanced in the Office action mailed

Applicants traverse the prior rejection, because 1) they question how the Examiner can argue that the requisite motivation exists to create the claimed invention, but that the invention has no patentable utility, and that one of skill would not know how to use the claimed invention; and 2) because the Office has failed to establish a *prima facie* case of obviousness, because there is no reasonable expectation of success to do that which Application has done, by modifying the cited references. Applicants argue that the Examiner has cited no motivation whatsoever for creating the claimed invention, that there is no suggestion in either references to arrive at the claimed invention. Furthermore, one of skill in the art would not have had a reasonable expectation of success, because Capecchi requires the knowledge of the genomic sequence and restriction mapping in order to create the targeting vector, and that Kubo teaches the cDNA of the ACTHR gene, and that because they do not teach the genomic DNA or restriction mapping, one would not know how to create the targeting vector. Thus, Applicants argue that the combination of the combined references do not teach each and every element of the claimed invention. See pp. 22-23 of the Response.

These arguments are not persuasive. The Examiner asserts that a reference can anticipate an invention without the reference teaching how to use it, within the meaning of 35 U.S.C. §101. See also *In re Schoenwald*, 22 USPQ2d 1671 (CA FC 1992). Thus, the combination of Capecchi and Kubo is found to be proper and is maintained for reasons of record. With regard to Applicants' argument for the "requirement" for genomic DNA and restriction mapping in order to create a targeting vector, it is acknowledged that Kubo teach a cDNA sequence, but there is no specific teaching in Capecchi that genomic DNA is a required component.

Art Unit: 1632

Indeed, as supported by Applicants' specification, a targeting construct only requires a DNA sequence that is homologous to the target gene of interest. See, for example, p. 8, lines 6-13. This homology can have varying degrees of sequence identity to the target gene. Thus, because Capecchi teaches methods of homologous recombination, and that sequences that are homologous will recombine with each other (see p. 38, 1st full ¶), Capecchi does not require specific knowledge of the genomic sequence, but that homologous sequences will also work in the taught methods. Accordingly, it is maintained that the combination of Capecchi and Kubo, are proper and provide sufficient motivation to arrive at the claimed invention.

Note that absent any phenotypic requirements of the claimed transgenic mice, the combination of the cited prior art is sufficient to make obvious the invention, further note that it would be well-known in the art that the disruption of any gene of interest, at any particular exon would have a reasonable expectation of decreased expression of that particular gene.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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